UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/046,278	01/16/2002	C. Jane Robinson	06478.1463	2377

22852 7590 12/26/2006

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	PAPER NUMBER
1651	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/26/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/046,278	ROBINSON ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8,10-17 and 20-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10-17 and 20-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/25/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/25/06 has been entered.

Claims 8, 10-17 and 20-30 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment/Arguments

Applicant's arguments with respect to claims 8, 10-17 and 20-30 have been considered but are moot in view of the new ground(s) of rejection owing to the amendments to the claims.

Claim Rejections - 35 USC § 112

Claims 20-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 20-28 are drawn to a method for treating angiogenesis or arteriogenesis in a patient in need thereof by administering purified α-AT3. The dependent claims are drawn to treatment of related diseases with the AT3 isoform. Claims 29 and 30 are drawn to the same treatment with the addition of β-AT3. Claims 29 and 30 are rejected insofar as they read on the administration of α-AT3.

The specification supports the in vivo administration of α-AT3 based on *in vitro* data of the inhibition of cell proliferation by α-AT3, pages 6-8. However, the prior art clearly demonstrates that such

in vitro results can not be extrapolated to in vivo therapy with any degree of certainty. Frebelius et al. (1996; cited in the IDS filed 8/25/06) disclose that "there was a discrepancy between the in vitro and in vivo findings." AT3 and both isoforms decreased the appearance of thrombin on injured vessel-walls in vitro (p. 7/15, center paragraph). However, Frebelius et al. teaches that "β-AT3 but not α-AT3 fully prevented the appearance of thrombin with coagulant activity after vessel-wall injury in vivo" (p. 9/15, 4th full paragraph).

The limited showing of in vitro data to support the treatment of angiogenesis or arteriogenesis and associated diseases by the administration of α-AT3 is not sufficient to enable claims drawn thereto. The prior art clearly establishes that α-AT3 is not effective to prevent smooth muscle proliferation in vivo and that such results were unexpected in light of promising in vitro data. the instant specification does not teach the skilled artisan how to overcome this significant obstacle. It would require undue experimentation for one of skill in the art to determine how to successfully treat angiogenesis or arteriogenesis and associated diseases by the administration of α-AT3 according to the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 8, 15 and 17 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Frebelius et al. (1996; cited in the IDS filed 8/25/06) in light of Wysocki et al. (1998).

Frebelius discloses that the aortas of living rabbits were subjected to balloon injury which resulted in thrombin coagulant activity on the injured blood vessels wall to cause fibrin formation. Saline

compositions comprising crude AT3, α-AT3 or β-AT3 (the latter two isoforms were purified by heparan affinity and purity was evaluated by screen electrophoresis, bottom of p. 5/15) were administered to the injured rabbits by an IV route. Control animals and animals receiving α-AT3 had significantly higher levels of thrombin on the aortic surface than animals receiving crude AT3 or β-AT3. Frebelius concluded that the inhibitory effect of AT on the appearance of thrombin coagulant activity on the injured vessel was is due to the β-AT3 content (p. 6-7/15, bridging paragraph).

Wysocki et al. disclose that the mechanical injury to a large artery of an animal is an experimental model for investigating vascular endothelial cell proliferation and angiogenesis in vivo. For example, inflated balloons can be used to remove endothelial cells in an artery, thus initiating smooth cell proliferation and angiogenesis (abstract and p. 225, both columns).

The disclosure by Frebelius meets the claim limitations because animals that undergo balloon-type injury to an artery are inherently experiencing angiogenesis because smooth muscle cells proliferate to overcome the loss of cells. Hence, the rabbits described by Frebelius are in need of therapy. Said rabbits receive purified β-AT3 by IV administration for therapy.

The disclosure by Wysocki et al. is a supporting reference and properly used in a rejection under of U.S.C. 102 since it describes the inherent relationship between balloon -mediated vessel injury and angiogenesis. MPEP 2131.01.

Claim Rejections - 35 USC § 102/103

Claims 8, 10-15 and 17 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over O'Reilly et al. (US 2002/0076413) or its equivalent O' Reilly et al. (US 6,607,724). For convenience, only O'Reilly et al. (US 2002/0076413) will be cited. These references were previously cited in the Office action mailed 10/30/2003.

O'Reilly et al. (US 2002/0076413) disclose at paragraph [0012] a method of inhibiting angiogenesis comprising administering a composition comprising a fragment, conformation, biological

equivalent or derivative of AT3. At paragraph [0057] glycosylation variants of AT3, along with β-AT3 are within the scope of the biological equivalents of AT3, as in instant claim 1. The proteins are partially or substantially purified [beginning of section [0057]), as in instant claims 1 and 17. The AT3 proteins can be made by recombinant (paragraphs [0063]-[0065], or transgenic means (claim 20 of the referenced patent), as in instant claim 14. The composition may further comprise a physiologically acceptable vehicle and can be administered orally, by injection, etc. (paragraph [0025]), as in instant claim 15. The method can be used to treat a disorder mediated by angiogenesis (paragraph [0018]), as in instant claim 1. Angiogenesis disorders include but are not limited to those enumerated at paragraph [0070] which include cancers, solid or blood borne tumors, tumor metastasis (as in instant claims 11 and 12), rheumatoid arthritis (instant claim 13), psoriasis (instant claim 13), macular degeneration, diabetic retinopathy (instant claim 10.

Hence, O'Reilly et al. (US 2002/0076413) clearly disclose treating angiogenesis related disorders by administering AT3 equivalents including β-AT3 that have angiogenesis antiproliferative properties.

Even if O'Reilly et al. (US 2002/0076413) does not anticipate the claimed invention expressly or inherently, it would still be obvious to use other antiangiogenic/antiproliferative forms of β-AT3 for the purpose of treating angiogenesis related disorders because this form is strongly suggested by O'Reilly et al. (US 2002/0076413).

Claim Rejections - 35 USC § 103

Claims 8 and 10-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Reilly (US 2002/0076413) in view of Antunes et al. (Int. J. Leprosy (June 2000) 68(2): 143; cited in the Office action mailed 10/29/04.

O'Reilly et al. (US 2002/0076413) discloses treating angiogenesis related disorders by administering AT3 equivalents including β-AT3 that have angiogenesis antiproliferative properties, as discussed *supra.*

O'Reilly does not disclose treating leprosy with active β-AT3.

Antunes et al. disclose that an investigation of the microvasculature of the cutaneous infiltrates of the skin of 39 patient afflicted with leprosy revealed an angiogenic component to the disease. Angiogenesis is mediated by the migration and proliferation of endothelial cells in the affected microvasculature. Antunes et al. state that the detection of angiogenesis in the cutaneous lesions of leprosy may bring about alternate and/or additional strategies for leprosy treatment (p. 143, left column and p. 149, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat leprosy with β-AT3. Antunes et al. discloses that leprosy has an angiogenic component that could be targeted in the treatment of leprosy. O'Reilly teaches that diseases that are associated with angiogenesis are suitable for therapy with β-AT3. Thus, the ordinary artisan would have been motivated to treat leprosy with β-AT3 because leprosy has an angiogenic component, Antunes et al. specifically suggest that treatment should be directed to the angiogenic component of the disease, and O'Reilly disclose that β-AT3 is suitable for treating diseases that are mediated by angiogenesis. The ordinary artisan would have had a reasonable expectation that β-AT3 would serve as an effective therapy for leprosy because O'Reilly have demonstrated that AT3 and its various forms are effective for treating diseases related to angiogenesis.

The following references are made of record to further establish the state of the art:

Frebelius, S. "Antithrombin III mediated inhibition of thrombin-induced proliferation in arterial smooth muscle cells: Functional differences between antithrombin III isoforms" Thromb. Haemost. (1995) 73: 102, abstract only.

Swedenborg, J. "The mechanisms of action of alpha- and beta-isoforms of antithrombin" Blood Coagulation Fibrinolysis (1998) 9(suppl. 3): S7-S10.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Susan Hanley
Patent Examiner
AU 1651

Leon B. Lankford, Jr.
Primary Examiner
Art Unit 1651